Procalcitonin, a new diagnostic and prognostic marker for severe infections

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INTRODUCTION

Morbidity and mortality attributed to severe bacterial infections are still major complications in modern medicine. Early recognition and prompt treatment can reduce morbidity and mortality. Better comprehension of the pathogenesis of sepsis and the response of the host organism have led to new definitions of sepsis (Table 1) [1]. Recent studies suggest that the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock represent different stages of the inflammatory response to infection [2].

Clinical diagnosis based on heart rate, respiratory rate, hypotension, fever, prostration and mental confusion is often difficult and non-specific. Parameters such as white blood cell (WBC) count, shift to the left in differential count, elevated C reactive protein (CRP) or increased erythrocyte sedimentation rate (ESR) can be useful, but are often not specific or sensitive enough. Table 2 shows the sensitivity, specificity and positive and negative predictive values for these tests. Cultures are often negative due to prior antimicrobial treatment or because adequate material is not readily available. The low sensitivity of blood cultures in the diagnosis of severe infections (range 17–69%) has led to the definition of culture-negative sepsis. This broad range in sensitivity is due to differences in defining and classifying the severity of infection. In a large prospective study, the outcome in patients with culture-negative septic shock was similar to that in patients with microbiologically proven septic shock [2]. Van Griethuysen et al reported a sensitivity and specificity of 53% and 83%, respectively, for temperature >38.5°C [3]. In our study population of 337 episodes, we calculated a sensitivity and specificity of 40% and 65%, respectively, using the threshold suggested by van Griethuysen et al [3] (unpublished data). The positive and negative predictive values for fever are given in Table 2.

The position of cytokines in the diagnosis and prognosis of severe infections is not yet defined and is controversial. Interleukin-6 (IL-6) is found earlier than CRP in severe infections, but it is not sensitive enough to serve alone in the diagnosis of severe infections [4,5]. Tumor necrosis factor (TNF) is known to rise early during acute bacterial infection, but declines rapidly after a peak of only a few hours, resulting in a low sensitivity [4,6]. There are few data available on other diagnostic parameters in the diagnosis of sepsis, such as phospholipase A_2, interferon-γ, neopterin or soluble CD14; too few episodes have been studied to allow definite conclusions, and often complicated laboratory procedures are required [6–9].

PROCALCITONIN

The CALC-I gene encoding the polypeptide hormone calcitonin was one of the first examples of tissue-specific expression of mRNA transcripts [10]. The human CALC-I gene contains six exons [11]. Its predominant product calcitonin, which regulates Ca^{2+}metabolism, is produced by thyroid C-cells, whereas other related peptides are found in neuronal cells. Calcitonin is generated by proteolytic separation

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Table 1 Definitions of the Consensus Conference of the American College of Chest Physicians [1]

Systemic inflammatory response syndrome (SIRS)

Two or more of the following:

1. Temperature >38°C or <36°C
2. Heart rate >90 beats/min
3. Respiratory rate >20 breaths/min
4. White blood cell count $>12.0\times10^9$/L, $<4.0\times10^9$/L, or >0.1 immature forms (bands)

Sepsis

SIRS plus a documented infection (positive culture for organism)

Severe sepsis

Sepsis associated with organ dysfunction, hypoperfusion abnormalities, or hypotension. (Hypoperfusion abnormalities include, but are not limited to, lactic acidosis, oliguria, or an acute alteration of the mental status)

Septic shock

Sepsis-induced hypotension despite fluid resuscitation plus hypoperfusion abnormalities

Culture-negative sepsis

SIRS plus empirical antibiotic treatment for a clinically suspected infection in which all cultures were negative

Culture-negative severe sepsis

SIRS associated with organ dysfunction, hypoperfusion abnormalities, or hypotension

Culture-negative septic shock

SIRS associated with hypotension despite fluid resuscitation plus hypoperfusion abnormalities. All cultures were negative, yet empirical antibiotic treatment for a clinically suspected infection was prescribed

Table 2 Sensitivity and specificity and negative and positive predictive value of temperature, WBC count, ESR, CRP, blood cultures and procalcitonin (PCT) in patients with sepsis

Text	Reference	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Blood culture	[2]	17–69	NA	NA	NA
	[42]	63	NA	NA	NA
Temperature >38.5°C	[3]	53	83	43	88
	UD	40	65	59	46
WBC $>12\times10^9$/L	[3]	73	32	18	85
	UD	55	67	29	86
ESR >30 mm/h	[43]	70	55	43	78
CRP >10 mg/L	[43]	67	69	51	81
	UD	42	68	38	72
PCT >0.5 ng/mL	[24]	0	79	61	78

UD, unpublished data; NA, not available.

from the larger prehormone, procalcitonin (PCT), which consists of 116 amino acids [12]. These peptides have already been used as markers in medullary thyroid carcinoma and in a number of other malignant processes [13–16]. In some of these cases, particularly lung cancer, PCT is found to be elevated without the presence of mature calcitonin. However, the biological role of this mechanism and the function of PCT remain unknown. The first hints about a mitogenic activity of PCT on human osteoblastic cells led to speculations about its use in patients with osteoporosis 17–20].

In healthy volunteers, PCT serum concentrations are below 0.15 ng/mL, although there may be a peak in the first day of life which is independent of an infectious stimulus [21,22]. The threshold value of PCT in patients with SIRS and suspected sepsis seems to be 0.5 ng/mL [23,24].

PCT is determined semi-automatically with an immunoluminometric assay using antibody-coated tubes in a luminometer. The test is specific for PCT, with a detection limit of 0.1 ng/mL and good reproducibility. The assay uses two monoclonal antibodies. One is a capture antibody directed against the 96–106 sequence in PCT, and the other is a tracer antibody directed against the 70–76 residues [21]. At room temperature a reduction in PCT plasma concentrations of 12.3% per 24 h is reported. There seems to be no significant influence of the blood sampling technique (arterial or venous line) or of repeated freezing–thawing cycles on the PCT concentrations [25].

As calcitonin and calcitonin-related peptides have been found in human neuroendocrine lung cells [26,27], efforts were first made to determine PCT in patients with inhalatory injuries following burns [28,29]. Here it is found at high concentrations without the presence of mature calcitonin. Higher concentrations of PCT correlated with mortality but not always with the burnt body-surface area. In some instances PCT remains elevated even after spirometry measurements return to normal values, indicating a long-term response of pulmonary neuroendocrine cells to burns [30]. In the same study, PCT and IL-6 concentrations were not associated with smoke inhalation or infection.

To investigate the role of PCT in severe infections, Dandona et al measured PCT concentrations in healthy volunteers after the injection of endotoxins derived from *Escherichia coli* [21]. TNF-α levels peaked very early after 90-min and fell to baseline levels after 6 h. IL-6 increased more gradually, peaking after 3 h and reaching the baseline concentration after 8 h. PCT peaked after 6 h and remained at a plateau for more than 24 h. In patients with bacterial and aspiration pneumonia, PCT is found to be only moderately elevated, correlating with the radiographic changes [31,32]. Values of up to 2 ng/mL are found on the first days of an episode.

There are only a few clinical studies investigating the position of PCT in the diagnosis and prognosis of infections. Assicot et al [33] were the first to report PCT serum levels in 79 pediatric patients; 19 of them had severe bacterial infection, with serum PCT concentrations ranging from 6 to 53 ng/mL. Patients with local infection or viral infection had lower values. They reported a close relation with infectious complications. We prospectively studied 337 adult patients admitted to an internal medicine department with suspected infection [24]. Patients who were classified as having SIRS had significantly lower PCT levels than patients with SIRS and in addition infection or septicemia or septic shock (Table 3). Other authors have found PCT levels above 1 ng/mL only in patients with septic shock. The causative organism (whether a Gram-negative or Gram-positive bacterium, or another microorganism such as a *Plasmodium* species or fungus) does not significantly influence the level of PCT in serum. Also, episodes with culture-negative sepsis are characterized by elevated PCT concentrations [34]. Immunocompromised patients (HIV infection or malignant diseases) also appear to show high serum PCT concentrations during sepsis, but leukopenia seems to be associated with lower PCT values after day 2 of the sepsis episode [23,24]. It has been reported that PCT may serve as a useful marker for the detection of systemic bacterial infection in patients with systemic autoimmune disease [35]. In the same study no correlation was seen between the degree of renal impairment and PCT concentrations.

Table 3 Maximum PCT values from days 0 and 1 in 337 patients with suspected sepsis [24]

Group	Mean PCT (ng/mL)	Standard deviation	No. of cases
1. SIRS only	0.6	2.2	215
2. SIRS + infection, microbiologically proven	6.6	22.5	53
3. SIRS + septicemia	8.5	19.0	49
4. SIRS + septic shock	34.7	68.4	20
Entire population	4.7	21.6	337

Data are also available on PCT concentrations in neonatal infections. There seems to be a normal peak PCT concentration in healthy newborns in the first few hours after birth, soon declining to baseline levels. The available data suggest that in neonates with severe infections PCT levels rise more rapidly than CRP levels and that the sensitivity is higher [22]. In pediatric patients PCT seems to distinguish better between bacterial and viral meningitis than CRP or an assay of cells and protein in cerebrospinal fluid [33,36].

There is limited information on PCT concentrations after surgical procedures. Efforts have been made to use PCT in the diagnosis of acute rejection of heart transplants. Patients with acute cellular rejection of the transplanted heart showed no circulating PCT; however, patients with bacterial or fungal infection showed moderate to high levels of PCT [37].

Elevated PCT levels have also been reported in tropical diseases. In patients with melioidosis due to *Burkholderia pseudomallei*, initial high PCT values have been reported to have prognostic value for higher mortality [38]. In Asian as well as European populations with malaria, PCT is elevated, reaching values over 100 ng/mL. This seems to correlate with severity. In the first few hours of infection, PCT values reach peak levels, declining rapidly under therapy [39,40].

Few data are available on the prognostic usefulness of PCT in patients with severe infections. In a study on 30 intensive care unit patients with sepsis or septic shock, PCT seemed to be higher in non-surviving patients than in survivors. CRP, TNF-α, neopterin, and IL-6 were not significantly correlated with the outcome of the infection [41]. In our study of 337 episodes, PCT levels were followed for 9 days. On admission, the mean PCT value for survivors was 4.4 ng/mL, whereas for non-survivors the mean values was 15.2 ng/mL $p=0.002$).

CONCLUSION

Although many tests are available in the diagnosis of severe infection, there is a need for more sensitive and specific diagnostic tools. The monitoring of success or failure of anti-infective therapy, especially in critically ill patients, is still unsatisfactory. Many studies have independently shown that PCT is elevated early in episodes of severe infections. However, there are large interindividual differences which seem not to be related to the disease. Differences in the definition of sepsis and severe infection may lead to conflicting results.

There are few statistically significant data on the threshold of PCT in diagnosis of severe infections, as most studies do not contain enough cases to lead to statistically established statements. The normal values for PCT in a healthy population are well established, but there are not enough studies on PCT values in patients with non-infectious diseases. The prognostic value of PCT needs to be established in larger study populations. The number of cases studied so far is limited, and it seems that if PCT is initially elevated and does not decline in the course of infection the mortality is higher. This is also the case in patients who do not respond to antimicrobial treatment. Multicenter studies are required to resolve these issues. The mechanism of elevated serum PCT levels in patients with severe infections is not well understood. However, it may be useful to elucidate the role of PCT in the pathologic mechanisms in severe infections, as this may lead to better utilization of this promising laboratory parameter.

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